



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION
OFFICE OF ESTICIDE PROGRAMS
REGISTRATION DIVISION (7505P)

MEMORANDUM

DATE: 17 OCTOBER 2016

SUBJECT: 2-Pyrrolidinone, 1-butyl; Human Health Risk Assessment and Ecological Effects Assessment to Support Proposed Exemption from the Requirement of a Tolerance When Used as an Inert Ingredient in Pesticide Formulations.

CAS Reg. No. 3470-98-2 PC Code 911157

FROM: Mark I. Dow, Ph.D., Senior Biologist
Chemistry, Inerts & Toxicology Assessment Branch (CITAB)
Registration Division (RD) 7505P

THROUGH: Kerry B. Leifer, Team Leader
CITAB/RD 7505P

TO: P.V. Shah, Ph.D., Branch Chief
CITAB/RD 7505P

I. EXECUTIVE SUMMARY

SciReg. Inc. (12733 Director's Loop, Woodbridge, VA 22192) submitted a petition (IN-10854) to the U.S. Environmental Protection Agency on behalf of Taminco U.S., Inc. a subsidiary of Eastman Chemical Company requesting the establishment of an exemption from the requirement of a tolerance for the compound 2-pyrrolidinone, 1-butyl (CAS Reg. No. 3470-98-2) as a food-use inert ingredient (solvent/co-solvent). The request is for establishment of the exemption from the requirement of a tolerance under 40 CFR § 180.920 for use in pesticide formulations applied to growing crops at a maximum concentration not to exceed 30% by weight in pesticide formulations. There are no other known existing uses of 2-pyrrolidinone, 1-butyl. The submitters Notice of Filing can be found in the public docket under EPA-HQ-OPP-2015-0655 at www.Regulations.Gov.

The oral LD₅₀ for 2-pyrrolidinone, 1-butyl- in the rat is greater than 300 mg/kg bw. The dermal LD₅₀ in the rat is > 2000 mg/kg bw. It is moderately irritating to the eye of New Zealand White rabbits. It is slightly irritating to the skin of New Zealand White rabbits. It is not a skin sensitizer in mice in the local lymph node assay.

A 90-day subchronic oral toxicity study was conducted with Wistar rats exposed to 2-pyrrolidinone, 1-butyl- via gavage dose of 0, 10, 100, and 500 mg/kg/day, according to OECD Test Guideline 408. The following effects were considered to be treatment-related and adaptive in nature and, therefore, not adverse: 1) the microscopic liver changes in animals of either sex treated with 500 mg/kg/day and males treated with 100 mg/kg/day, and the associated blood chemistry changes identified in animals of either sex treated with 500 mg/kg/day were likely to represent an adaptive response to treatment 2) the microscopic changes in the adrenals of males treated with 500 and 100 mg/kg/day and the microscopic thymus changes are likely the result of the adaptive changes apparent in the liver or a secondary stress related response. Therefore the NOAEL is 500 mg/kg/day.

Prenatal development toxicity was conducted with 2-pyrrolidinone, 1-butyl-, in accordance with OECD Test Guideline 414 using Pregnant CrI:CD(SD) rats exposed to the test item at concentrations of 0, 5, 50, or 500 mg/kg/day by oral gavage. Maternal toxicity was manifested as decreased food consumption and weight loss on days 6 to 19 of gestation at 500 mg/kg/day. Developmental toxicity was manifested as decreased fetal weight in female fetuses at the same dose as maternal toxicity, 500 mg/kg/day. There was no evidence of fetal susceptibility. The NOAEL for administration of 2-pyrrolidinone, 1-butyl- was determined to be 50 mg/kg/day.

Since there is a wide dose spread in the developmental toxicity study in rats, a benchmark dose (BMD) modeling was conducted using decreased fetal weight as an adverse effect. The BMD value is 306 mg/kg/day and the average BMDL is 201 mg/kg/day for a 5% response in decreased fetal body weight.

Carcinogenicity data are not available for 2-pyrrolidinone, 1-butyl-. In the 90-day toxicity study, the liver, kidney, thymus, and adrenals were target organs, however, the effects noted were considered as an adaptive response at the dose levels tested. Evaluation of the database for N-methylpyrrolidone (NMP) shows similar target organ toxicity as 2-pyrrolidinone, 1-butyl- and 1-ethylpyrrolidin-2-one (NEP), as both chemicals are considered suitable surrogates for evaluation. Neither 2-pyrrolidinone, 1-butyl-, N-methylpyrrolidone, nor 1-ethylpyrrolidin-2-one was found to be genotoxic or mutagenic in a number of assays. In carcinogenicity studies, N-methylpyrrolidone was not carcinogenic in two-year rat studies by the inhalation and dietary routes of exposure. An increased incidence of liver adenomas and carcinomas was seen in mice exposed to a dietary level of N-methylpyrrolidone exceeding 1,000 mg/kg/day for 18 months. Based on the lack of mutagenicity or genotoxicity and the similarity of 2-pyrrolidinone, 1-butyl- to n-methylpyrrolidone, it can be concluded that 2-pyrrolidinone, 1-butyl- is unlikely to be carcinogenic at anticipated levels of dietary exposure.

The mutagenic potential of 2-pyrrolidinone, 1-butyl- was assessed in the *Salmonella typhimurium* reverse mutation assay, mammalian cell gene mutation and micronucleus tests. 2-Pyrrolidinone, 1-butyl- was negative in all assays. Therefore, 2-pyrrolidinone, 1-butyl- is not considered mutagenic nor clastogenic.

There were no studies/data directly related to the possible neurotoxicity of 2-pyrrolidinone, 1-

butyl. However, evidence of potential neurotoxicity was not observed in functional observation battery (FOB) performed in the 90-day oral toxicity study of 2-pyrrolidinone, 1-butyl in the rat. Therefore, pyrrolidinone, 1-butyl is not expected to be neurotoxic.

There were no studies/data directly related the immunotoxicity of 2-pyrrolidinone, 1-butyl. Thymic atrophy was observed at >100 mg/kg/day in rats treated with 2-pyrrolidinone, 1-butyl in the 90-day oral toxicity study, however, these microscopic changes in the thymus are considered as an adaptive response and not an adverse effect.

There were no studies/data directly related to the metabolism, of 2-pyrrolidinone, 1-butyl.

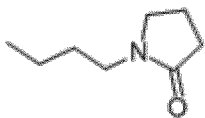
2-Pyrrolidinone, 1-butyl- exhibits low toxicity to aquatic organisms and is not expected to bioaccumulate or be persistent in the environment.

The mammalian toxicity and environmental fate and effects data are adequate to derive a regulatory decision. Based on the toxicological information and based upon the Agency's screening level assessments of human exposure and risk, the Agency approves of 2-pyrrolidinone, 1-butyl as an inert ingredient (solvent/cosolvent) (CAS Reg. No. 3470-98-2) under 40 CFR 180.920 (inert ingredients use pre-harvest: exemptions from the requirements of a tolerance) at a maximum concentration not to exceed 30% w/w in pesticide formulations.

II. INTRODUCTION

On August 12, 2015, SciReg. Inc. (12733 Director's Loop, Woodbridge, VA 22192) submitted a petition (IN-10854) to the U.S. Environmental Protection Agency on behalf of Taminco U.S., Inc. a subsidiary of Eastman Chemical Company (Two Windsor Plaza, Suite 400, 7540 Windsor Drive, Allentown, PA 18195) requesting the establishment of an exemption from the requirement of a pesticide tolerance for the compound 2-pyrrolidinone, 1-butyl (CAS Reg. No. 3470-98-2) as a food-use inert ingredient (solvent/co-solvent). Specifically, the submission requests the establishment of an exemption from the requirement of a tolerance under 40 CFR § 180.920 for residues of 2-pyrrolidinone, 1-butyl when used in pesticide formulations applied to growing crops only at a maximum concentration not to exceed 30% by weight in pesticide formulations. There are no other known existing uses of 2-pyrrolidinone, 1-butyl. The submitters Notice of Filing may be found in the public docket under EPA-HQ-OPP-2015-0655 at www.Regulations.Gov.

III. PHYSICAL/CHEMICAL PROPERTIES MRID 49695101



Chemical Structure

Chemical Name: 2-pyrrolidinone, 1-butyl

CAS Reg. No.: 3470-98-2

Synonyms: 1-butyl-2-pyrrolidinone (IUPAC name)

n-Butylpyrrolidinone

N-Butylpyrrolidone

Molecular formula: C₈H₁₅NO
Molecular weight: 141 g/mol

Table 1.0

Parameter	Result	Reference
Appearance	Clear liquid	MRID 49695101
Density	0.96 g/cm ³	
Vapor Pressure	35 Pa @ 20° C	
Boiling Point	241° C	
Melting Point	< -75° C	
Octanol/water partition Coefficient	Log P _{OW} = 0.73	
Water Solubility	Fully miscible	
pH	7.65 (10% aqueous solution)	
Log P _{OW}	1.265± 0.003	MRID 49695102

IV. TOXICOLOGICAL SUMMARY

Table 2.0

Test	Result	Reference
Acute oral toxicity	OECD 423 300 mg/kg < LD ₅₀ < 2000 mg/kg	MRID 49695110 Harlan Labs. Study No. D41574; Vol 10
Acute dermal toxicity	OECD 402 LD ₅₀ > 2000 mg/kg	MRID 49695111 Harlan Labs. Study No. 414001170; Vol 11
Eye Irritation	OPPTS 870.2400 Moderate irritation	MRID 49695112 Charles River Labs. Study No. 20054210; Vol 12
Dermal Irritation	OPPTS 870.2500 Slight irritant	MRID 49695113 Charles River Labs. Study No 20050801 20050801; Vol 13
Dermal Sensitization	OECD 429; There were significant Deviations from the OECD Guideline as well as significant concerns with the quality of the work Therefore the sponsor repeated the study. OECD 429 (second study) negative	MRID 49695115 LPT Lab. Of Pharmacol. & Toxicol. GmbH & Co. KG study No. 41500248; Vol 15
Genotoxicity	Bacterial reverse mutation OECD 471: negative	MRID 49695116 LPT Lab. Of Pharmacol. & Toxicol. GmbH & Co. KG

		Study No. 29175; Vol 16
	<i>in vitro</i> mammalian cell gene mutation (OECD 476) negative	MRID 49695117 Harlan Labs. Ltd. Study No. 41303952; Vol 17
	<i>in vitro</i> mammalian cell micronucleus test (OPPTS 870.5300) negative	MRID 49695118 Harlan Labs. Ltd. Study No 41303962; Vol 18
90-day oral – rat	OECD 408 NOAEL = 500 mg/kg/day males and females	MRID 49695119 Harlan Labs. Ltd. Study No. 41303953; Vol 19
Prenatal development – oral rat	OECD 414 NOAEL Dams = 50 mg/kg/day Fetuses > 500 mg/kg/day	MRID 49695120 LPT Lab. Of Pharmacol. & Toxicol. GmbH & Co. KG Study No. 29197; Vol 20
Carcinogenicity	Not potentially carcinogenic	MRID 49695123 VJP Consulting, Inc. Vol 23

Acute Oral Toxicity

2-Pyrrolidinone, 1-butyl- was tested for acute oral toxicity in WIST (SPF) rats according to OECD Guideline Test 423 and in compliance with the Swiss Ordinance relating to Good Laboratory Practice which is based on OECD Good Laboratory Practice.

Three female RccHan: WIST (SPF) rats were treated with the test item, 2-pyrrolidinone, 1-butyl-, by oral gavage at a dose of 2,000 mg/kg bw and two further groups of three females each were treated with 300 mg/kg bw of the test item. The test item was formulated in purified water at a concentration of 0.2 g/mL and 0.03 g/mL and administered at a dose volume of 10 mL/kg.

All animals were examined for clinical signs approximately 30 minutes after treatment and again at approximately 1, 2, 3, and 5 hours after treatment on Day 1, and once daily during test Days 2 - 15. Mortality/viability was recorded together with clinical signs twice daily during Days 2 - 15. Body weights were recorded on Day 1 (prior to administration) and on Days 8 and 15. All animals were necropsied and examined macroscopically.

All animals treated with 300 mg/kg bw of 2-pyrrolidinone, 1-butyl- survived until the end of the study period. Two females treated with 2,000 mg/kg bw of the test item died after the administration and one of them was sacrificed in extremis also on the day of treatment. The females treated with 2,000 mg/kg bw showed shortly after treatment moderate convulsions, tachypnea, prostration, clear lacrimation in both eyes, and were found unconscious; two of them were found dead later. The females treated with 300 mg/kg bw of the test item had slightly to moderately decreased activity and slightly ruffled fur. The three further females treated with 300 mg/kg bw had no clinical signs. No clinical signs were observed during Days 2 to 15. The body weight of the animals was within the range commonly recorded for this strain and age. No macroscopic findings were recorded at necropsy. The median lethal dose of 2-pyrrolidinone, 1-

butyl- after single oral administration to female rats, observed over a period of 14 days is: 300 mg/kg bw < LD50 (female rat) < 2,000 mg/kg bw (Damme, 2013, MRID 49695110)

Acute Dermal Toxicity

The test item, 2-pyrrolidinone, 1-butyl-, was tested for acute dermal toxicity in Wistar (RccHanTM:WIST) rats according to OECD Test Guideline 402 and in compliance with OECD Good Laboratory Practice.

Initially, two animals (one male and one female) were given a single, 24 hour, semi-occluded dermal application of the undiluted test item to intact skin at a dose level of 2,000 mg/kg bw. Based on the results of the initial test, a further group of eight animals (four males and four females) were similarly treated. Clinical signs and body weight development were monitored during the study. The test sites were examined for evidence of primary irritation once daily for fourteen days. All animals were subjected to gross necropsy.

There were no deaths and no signs of systemic toxicity. Very slight erythema was noted at the test sites of two females. Small superficial scattered scabs and glossy skin were also noted at the test site of one female. No other signs of dermal irritation were noted. Animals showed expected gains in body weight except for two females which showed no gain in body weight or body weight loss during the first week with expected gain in body weight during the second week. No abnormalities were noted at necropsy. Therefore, the acute dermal LD₅₀ for 2-pyrrolidinone, 1-butyl- was greater than 2,000 mg/kg bw (Bradshaw, 2014; MRID 49695111).

Primary Eye Irritation

2-Pyrrolidinone, 1-butyl- was tested for acute ocular irritation in three male New Zealand White rabbits according to OPPTS Guideline Test 870.2400 and in compliance with EPA (40 CFR Parts 160 and 792) and OECD Good Laboratory Practice.

Each of three rabbits received a single 0.1 mL dose of the test substance, 2-pyrrolidinone, 1-butyl-, in the conjunctival sac of the right eye. The contralateral eye of each animal remained untreated and served as a control. Test and control eyes were examined for signs of irritation for up to 10 days following dosing. Animals were observed for general health/mortality and moribundity twice daily throughout the study.

Exposure to the test article produced corneal opacity in 1/3 test eyes by the 24 hour scoring interval and complete resolution occurred by the Day 7 scoring interval. Iritis was observed in 1/3 test eyes by the 1 hour scoring interval and in 2/3 test eyes by the 24 hour scoring interval. Complete resolution of the iritis occurred in 1/3 test eyes by the Day 7 scoring interval and in 2/3 test eyes by the Day 10 scoring interval. Conjunctivitis (redness, swelling, and/or discharge) occurred in 3/3 test eyes by the 1 hour scoring interval and complete resolution occurred in 1/3 test eyes by the Day 7 scoring interval and in 2/3 test eyes by the Day 10 scoring interval. An additional ocular finding of neovascularization (2/3 test eyes) was noted during the study. Decreased fecal output was observed in all animals. This observation, which is a known pharmacological effect of opioids, was likely due to the buprenorphine treatment that the animals received from Days 0 to 5. According to the Kay and Calandra Evaluation Criteria, 2-

pyrrolidinone, 1-butyl- is considered to be a moderate irritant to the ocular tissue of the rabbit (Hohenbrink, 2014a, MRID 49695112).

Primary Dermal Irritation

2-Pyrrolidinone, 1-butyl- was tested for acute skin irritation in three male New Zealand White rabbits according to OCSPP Test Guideline 870.2500 and in compliance with EPA (40 CFR Parts 160 and 792) and OECD Good Laboratory Practice.

Each of three rabbits received a 0.5 mL dose of the test substance, 2-pyrrolidinone, 1-butyl-, as a single dermal application. The dose was held in contact with the skin under a semi-occlusive binder for exposure periods of 3 minutes, 1 hour, and 4 hours for one animal and an exposure period of 4 hours for two animals. Following the completion of each exposure period, the binder was removed and the remaining test substance was wiped from the skin using gauze moistened with deionized water followed by dry gauze. Test sites were subsequently examined and scored for dermal irritation for up to 21 days following patch removal.

Three-Minute Exposure: Exposure to the test substance produced no erythema or edema through 72 hours post-dose; however, very slight erythema was noted at the single test site on Day 14, which subsequently resolved by Day 21.

One-Hour Exposure: Exposure to the test substance produced very slight erythema at the single test site immediately after patch removal. The dermal irritation was not observed at the 1-hour scoring interval, but was present again at the 24-, 48-, and 72-hour scoring intervals. The dermal irritation was not observed on Day 7, but was observed again on Day 14. Day 21 scoring revealed no irritation. Additional dermal findings included desquamation.

Four-Hour Exposure: Exposure to the test substance produced very slight erythema at 3/3 test sites and very slight edema at 1/3 test sites by the 1-hour scoring interval. Well-defined erythema was observed in 1/3 test sites at the 24-, 48-, and 72-hour scoring intervals. The dermal irritation was not observed in 1/3 test sites on Day 7, but was again observed in that animal on Day 10. Dermal irritation did not resolve completely in the remaining two test sites. Additional dermal findings included blanching (focal and/or pinpoint areas up to 10% of the test site) in 1/3 test sites and desquamation in 3/3 test sites. Under the conditions of the test (4-hour exposure), 2-pyrrolidinone, 1-butyl- is considered to be a slight irritant to the skin of the rabbit. The calculated Primary Irritation Index (P.I.I.) for the test substance was 1.33 (Hohenbrink, 2014b, MRID 49695113).

Dermal Sensitization

Two dermal sensitization studies were conducted with 2-pyrrolidinone, 1-butyl-. A local lymph node assay in mice was previously conducted at LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG ("LPT") in April 2013. Subsequent review of this study (by the submitter) revealed significant deviations from the OECD Guideline Test 429, as well as significant concerns with the quality of the work. Per the Guideline, a laboratory may deviate from a requirement when there is a valid reason which should be stated and supported in the final report. In the case of the LPT Study, there were a number of significant deviations from the Guideline that were not supported in the final report including, but not limited to the following:

- Use of lymph node weight as the metric for cellular proliferation instead of more sensitive metrics such as radiolabeled thymidine as prescribed by the Guideline or flow cytometric analysis of isolated cells.
- Use of a customized Stimulation Index instead of the index specified by the Guideline.
- Study duration of four days instead of six days as specified by the Guideline.

Each of these deviations from the Guideline is significant and was not justified by the laboratory. The most conspicuous example involves the reproducibility of the results wherein certain concentrations of the test article that were not irritating in the range finder were subsequently found to be irritating in the actual study. The inability of the laboratory to reproduce findings for a simple endpoint raises significant concerns regarding the quality of work done in performance of this study.

Given the significant deviations from the Guideline and the concerns regarding the quality of the of this first study, a second local lymph node assay in the mouse was conducted in accordance with the OECD Guideline Test 429. Both dermal sensitization studies are summarized below.

Dermal Sensitization Study #1

The test item, 2-pyrrolidinone, 1-butyl-, was assessed for skin sensitization potential in female NMRI mice, using the local lymph node assay.

This study did not employ the use of radioactive labelling to measure cell proliferation. An alternative method was used employing lymph node weight and lymph node cell count. This method was established by a European inter-laboratory validation exercise. In addition, the acute inflammatory skin reaction was measured by ear weight determination of circular biopsies of the ears and ear thickness measurements on test day one and test day four to identify skin irritation properties of the test item. Values above 1.4 (lymph node cell count to identify sensitization) or 1.1 (ear weight to identify irritation) were considered positive.

Five concentrations of the test item (1%, 5%, 10%, 25%, and 50% w/w) diluted with acetone/olive oil (3+1 v/v) were tested in six female NMRI mice per group and compared to a vehicle control group. In addition, a positive control group [25% solution v/v of α -hexyl cinnamic aldehyde in acetone/olive oil (3+1 v/v)] was tested.

The positive control group caused the expected increases in lymph node cell count and lymph node weight (statistically significant at $p \leq 0.01$). Therefore, the study was regarded as valid.

Treatment with 2-pyrrolidinone, 1-butyl- at concentrations of 1% and 5% did not reveal statistically significant increased values for lymph node cell count and lymph node weight. The stimulation indices of the lymph node cell count did not exceed the threshold level of 1.4. Therefore, the test item was classified as not sensitizing. The threshold level for the ear weight of 1.1 was not exceeded and no increase of ear thickness was observed.

Treatment with 2-pyrrolidinone, 1-butyl- at concentrations of 10, 25, and 50% (w/w) revealed statistically significant increased values ($p \leq 0.01$ or $p \leq 0.05$) for lymph node cell count and

lymph node weight. However, ear weights were also significantly increased at these concentrations pointing to strongly irritating properties on the mouse ear. The stimulation indices of the lymph node cell count (sensitizing properties) and ear weight (irritation properties) exceeded the threshold levels of 1.4 or 1.1.

No signs of local or systemic intolerance were recorded. Body weight was not affected by the treatment.

2-Pyrrolidinone, 1-butyl- did not reveal any sensitizing properties in the local lymph node assay at concentrations of 1% or 5% (w/w) in acetone/olive oil (3 + 1 v/v). Concentrations of 10% or higher did not permit an evaluation due to the irritating properties of the test item shown through increased ear weight and an increase in ear thickness (Haferkorn, 2013, MRID 49695114).

Dermal Sensitization Study #2

The test item, 2-pyrrolidinone, 1-butyl-, was assessed for skin sensitization potential in CBA/Ca strain mice using the local lymph node assay according to OECD Test Guideline 429 and in compliance with OECD Good Laboratory Practice.

Following a preliminary screening test in which no clinical signs of toxicity were noted at a concentration of 50% v/v, this concentration was selected as the highest dose investigated in the main test of the local lymph node assay. Three groups, each of five animals, were treated with 50 µL (25 µL per ear) of the test item as a solution in acetone/olive oil 4:1 at concentrations of 50%, 25% or 10% v/v. A further group of five animals was treated with acetone/olive oil 4:1 alone. A concurrent positive control test, using a group of five animals, was also performed with the known sensitizer, α -hexylcinnamaldehyde tech., 85%, at a concentration of 25% v/v in acetone/olive oil 4:1. The test item was applied topically to the dorsal surface of the ear.

The Stimulation Index expressed as the mean radioactive incorporation for each treatment group divided by the mean radioactive incorporation of the vehicle control group was as follows: 0.70, 0.91, and 1.22 for the 10%, 25%, and 50% treatment groups, respectively. The Stimulation Index for the positive control was 5.39.

Therefore, the test item was considered to be a non-sensitizer under the conditions of the test. α -Hexylcinnamaldehyde, tech., 85% gave a Stimulation Index of greater than 3 when tested at a concentration of 25% v/v in acetone/olive oil 4:1 (Henzel, 2015; MRID 49659115).

Developmental toxicity.

In a developmental toxicity study (MRID 49695120, Hansen, 2013), 2-pyrrolidinone, 1-butyl was administered by gavage in tap water to 25 mated female CD[®] CrI: CD (SD) rats/dose at dose levels of 0, 5, 50, or 500 mg/kg bw/day (dosing volume of 5 mL/kg bw) on gestation days (GDs) 6-19, inclusive. At scheduled sacrifice on GD 20, animals were laparotomized to determine pregnancy status and/or viability of the litter until twenty litters with live young were obtained for each group. The remaining females were discarded, unexamined. The selected pregnant animals were fully necropsied, and gravid uterine weights, corpora lutea counts, and the numbers and positions of implantations, live and dead fetuses, and resorptions were recorded. All fetuses were weighed individually, sexed, and examined for external anomalies. One-half of the fetuses from each litter

were designated for skeletal examination, and the remaining one-half of the fetuses were subjected to visceral examination. All placentae were counted, individually weighed, and examined grossly.

High-dose dams had significantly decreased food consumption on GDs 7 and 8 (23% and 10% less than controls, respectively) and a related mean weight loss (~6 g) during GD 6-7, with 15/20 dams losing weight (vs. 5/20 controls). Mean body weight gains of the high-dose group were decreased over the GD 6-9 interval (-72%; $p<0.01$), during GDs 12-15, 15-18, and 18-20 (11-15% less than controls; n.s.), and for the overall GD 6-20 treatment interval (-19%; $p<0.01$). As a result, the high-dose dams had slight, but statistically significant, decreases in mean absolute body weight on GD 7, GDs 13-14, and GDs 16-20. The differences seen later in the study were due in part to decreased gravid uterine weights (-11%; n.s). However, the adjusted (for gravid uterus) GD 6-20 body weight change remained significantly decreased (-39% $p<0.01$). The decreased gravid uterine weights in high-dose dams were associated with decreased placental weights (male fetuses: -9%, $p<0.05$; female fetuses: -12%, $p<0.01$) as well as decreased fetal weight (females only). **The maternal LOAEL in rats is 500 mg/kg/day, based on transiently decreased food consumption and decreased absolute body weights. The maternal NOAEL is 50 mg/kg/day.**

Developmental toxicity was evident at the high dose as significantly decreased placental weights (mentioned above) and significantly decreased fetal weights in female fetuses ($p<0.01$). The mean numbers of corpora lutea, implantations, and viable fetuses of the treated dams were similar to those of controls. There were no treatment-related effects on pre- or post-implantation loss or fetal sex ratio. Maternal treatment did not increase the incidences of malformations, variations, and/or retardations. **The developmental LOAEL in rats is 500 mg/kg/day based on decreased fetal weight in female fetuses. The developmental NOAEL is 50 mg/kg/day.**

Benchmark Dose (BMD) Modeling for 2-Pyrrolidinone, 1-butyl.

Toxicology Excellence for Risk Assessment (TERA) evaluated the critical effects of 2-pyrrolidinone, 1-butyl- in a range-finding and a prenatal developmental study in CD rats to 1) determine the key study with data appropriate for conducting benchmark dose (BMD) modeling, 2) identify the data for modeling, and 3) conduct the modeling.

Initial modeling was conducted using the continuous models in U.S. EPA's BMD modeling software (BMDS version 2.5.0) for the mean and individual data for fetal body weights and gravid uterine weights. A benchmark response (BMR) of 5%, the standard BMR for developmental toxicity studies was modeled along with one standard deviation for comparison. Several of the models for the BMR of 5% and one standard deviation model runs fit the data well, and criteria for all of these models were comparable. The ranges of BMDs and benchmark dose model lower confidence limits (BMDLs) varied from 196 to 308 mg/kg-day. An average within these ranges would be an acceptable choice for a point of departure. For a BMR of one standard deviation, the average BMD is 394 mg/kg/day and the average BMDL is 250 mg/kg/day. For a BMR of 5%, the average BMD is 306 mg/kg/day and the average BMDL is 201 mg/kg/day. In this case, the BMDL of 201 mg/kg-day for a 5% response is recommended because the modeling was based on a BMR of 5% decreased fetal body weight, which is more biologically appropriate than the use of one standard deviation (Parker and Dourson, 2015, MRID 49695121).

90-day Subchronic Toxicity.

A 90-day subchronic oral toxicity study was conducted with the test item, 2-pyrrolidinone, 1-butyl-, according to OECD Test Guideline 408 and in compliance with OECD Good Laboratory Practice.

Ten male and ten female Wistar HanTM:RccHanTM:WIST strain rats were assigned to each dose level (0, 10, 100, and 500 mg/kg/day) and were administered vehicle (distilled water) or test item daily by oral gavage for ninety days. Animals were observed daily, and body weight, food consumption, and functional observations were recorded weekly for all animals. Estrous cycle was evaluated for all females during the last three weeks of the study. After 13 weeks of treatment, ophthalmoscopic exams were conducted on the control and high dose animals, and hematology and chemistry, were analyzed for all animals. At termination, all animals were sacrificed and necropsied. All animals were subject to macroscopic examination and select organ weights were taken. Males were also subject to sperm assessment. Microscopic examination was performed on select tissues from all animals in the control and high dose groups. Also, the liver and thymus were examined from all animals in the low and intermediate dose groups, and the kidney was examined from males only in the low and intermediate dose groups.

No mortality was observed with treatment of 2-pyrrolidinone, 1-butyl- up to 500 mg/kg/day. Neither the type, incidence or distribution of clinical signs indicated an adverse effect of treatment at 10, 100, or 500 mg/kg/day. There were no toxicologically significant changes in the behavioral parameters measured, functional performance or sensory reactivity at 10, 100, or 500 mg/kg/day. There were no adverse effects of treatment on body weight development, food consumption or food efficiency, or water consumption at 10, 100, or 500 mg/kg/day. There were no treatment-related ocular effects and no adverse effects were detected during the estrous cycle assessments or in sperm concentration, morphological assessments, or in homogenization-resistant spermatid counts. There were no toxicologically significant effects of treatment on the hematology parameters measured. Males treated with 500 mg/kg/day showed a statistically significant increase in total protein, calcium, creatinine, and bile acid, and a statistically significant reduction in albumin/globulin ratio. Females treated with 500 mg/kg/day showed a statistically significant reduction in albumin/globulin ratio, chloride, and alkaline phosphatase and a statistically significant increase in cholesterol, bilirubin, and bile acid. Males treated with 100 mg/kg/day showed a statistically significant increase in chloride. Eight males treated with 500 mg/kg/day had enlarged livers at necropsy. No toxicologically significant macroscopic findings were evident in females treated with 500 mg/kg/day or in animals of either sex treated with 10 or 100 mg/kg/day. Animals of both sexes treated with 500 mg/kg/day and males treated with 100 mg/kg/day had a statistically significant increase in kidney and liver weights, both absolute and relative to terminal body weight. No such effects were evident in females treated with 100 mg/kg/day or animals of either sex treated with 10 mg/kg/day. Liver hypertrophy or centrilobular hypertrophy was observed in males and females treated with 500 mg/kg/day and in males treated with 100 mg/kg/day. An increase in incidence and severity of hyaline droplet accumulation, multifocal basophilic tubules (degenerating/regenerating), and the presence of proteinaceous casts in the tubules of kidneys of males were observed at 100 mg/kg/day and above. Minimal atrophy in the thymus was noted in males (3-6/10) and females (5/10) treated with 500 mg/kg/day and in males treated with 100 mg/kg/day. Vacuolation in the adrenal cortex was present in males only at an increased incidence (9/10) and severity (minimal to mild) at 100 mg/kg/day and above. One male treated with 10

mg/kg/day had vacuolation above the expected level; however, the toxicological significance of this in only one male is equivocal.

Oral administration of 2-pyrrolidinone, 1-butyl- to rats by gavage for a period of ninety consecutive days, resulted in treatment related effects in animals of either sex treated with 500 mg/kg/day and males treated with 100 mg/kg/day. The NOEL was considered to be 10 mg/kg/day for males and 100 mg/kg/day for females. The following effects were considered to be treatment-related and adaptive in nature and, therefore, not adverse: 1) the microscopic liver changes in animals of either sex treated with 500 mg/kg/day and males treated with 100 mg/kg/day, and the associated blood chemistry changes identified in animals of either sex treated with 500 mg/kg/day were likely to represent an adaptive response to treatment and, therefore, considered not to represent a serious risk to health, 2) the microscopic changes in the adrenals of males treated with 500 and 100 mg/kg/day and the microscopic thymus changes are likely the result of the adaptive changes apparent in the liver or a secondary stress related response. In terms of extrapolation to man, and risk assessment calculations, the effects relating to renal changes in the male rat are species- and sex-specific and, therefore, are not relevant. For these reasons, the NOAEL was considered to be 500 mg/kg/day for animals of either sex (Wakefield, 2014. MRID 49695119).

Carcinogenicity

The 90-day toxicity study in rats (MRID 49695119) provided a basis for evaluation of the carcinogenic potential of 2-pyrrolidinone, 1-butyl-. In that study, the liver, kidney, thymus, and adrenals were target organs for toxicity. Evaluation of the toxicity database for N-methylpyrrolidone (NMP) shows similar target organ toxicity as 2-pyrrolidinone, 1-butyl- and 1-ethylpyrrolidin-2-one (NEP), as both chemicals are considered suitable surrogates for evaluation. Neither 2-pyrrolidinone, 1-butyl-, N-methylpyrrolidone, nor 1-ethylpyrrolidin-2-one was found to be genotoxic or mutagenic in a number of assays. In carcinogenicity studies, N-methylpyrrolidone was not carcinogenic in two-year rat studies by the inhalation and dietary routes. An increased incidence of liver adenomas and carcinomas were seen in mice exposed to a dietary level of N-methylpyrrolidone exceeding 1,000 mg/kg/day for 18 months. No tumors were seen at lower concentrations. Liver tumor induction in mice and its relevance to humans has been an area of great debate for decades. A mode of action study with N-methylpyrrolidone at the high dose used in the mouse oncogenicity study strongly suggests that exposure to N-methylpyrrolidone at high concentrations leads to a mitogenic burst in the mouse liver that ultimately may lead to a tumorigenic response in the liver. This mode of action has been proposed for phenobarbital. Based on the lack of mutagenicity or genotoxicity and the similarity of 2-pyrrolidinone, 1-butyl- to N-methylpyrrolidone, it can be concluded that 2-pyrrolidinone, 1-butyl- should not be considered as potentially carcinogenic. Further, liver changes seen in the studies were considered as adaptive, nonadverse findings. Kidney pathological lesions were consistent with hydrocarbon nephropathy in male rats induced by α -2-microglobulin accumulation, a finding that is considered as not relevant to humans. The only evidence of a tumorigenic response was seen at an exceedingly high dose in mice treated with N-methylpyrrolidone

Bacterial Reverse Mutation Study

In a reverse gene mutation assay in bacteria (MRID 49695116, Flugge, 2012), *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 were exposed to test article n-

butylpyrrolidone (CAS Reg. No 3470-98-2) (99.3% a.i., Batch No. 120913_639), dissolved in acetone, without and with S9 activation, in a plate incorporation assay and in a pre-incubation assay. The concentrations used for both assays were: 0, 31.6, 100, 316, 1000, 3160 and 5000 µg/plate for all tester strains, without and with activation. Three plates/test condition were used in both experiments. The S9 fraction was prepared in-house from livers of Aroclor 1254-induced rats (strain, sex and age not reported). The S9-mix contained 5% v/v of the S9 fraction, which contained 33.1 mg protein/mL.

The test article was tested up to a limit concentration of 5000 µg/plate. No cytotoxicity was noted under any test condition up to the limit concentration, and there was no precipitation of the test article. The number of revertants per plate was not increased over the concurrent solvent control value at any test article concentration, up to the limit concentration, without or with S9-mix, in any tester strain, in either experiment. The solvent and positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

***In Vitro* Mammalian Cell Gene Mutation Test**

In an *in vitro* mammalian cell gene mutation assay at the thymidine kinase (TK) locus (MRID 49695117, Brown, 2014), mouse lymphoma L5178Y cells cultured *in vitro* were exposed to test article N-butylpyrrolidone (CAS Reg. No 3470-98-2) (99.7% a.i., batch number 01061301) dissolved in RPMI 1640 culture medium for 4 hours at concentrations of 0, 44.1, 88.2, 176.4, 352.8, 705.6 and 1411.2 µg/mL without and with activation in the first mutation experiment and at concentrations of 0, 44.1, 88.2, 176.4, 352.8, 705.6 and 1411.2 µg/mL for 24 hours in the absence of metabolic activation and for 4 hours with activation, in the confirmatory mutation experiment. The concentration of 1411.2 µg/mL is the limit concentration of 10 mM, which applies when there is neither cytotoxicity nor insolubility. The S9 fraction was obtained from livers of male Sprague-Dawley rats (weighing *ca.* 250 g) that had each received three consecutive daily oral doses of phenobarbital/β-naphthoflavone (80/100 mg/kg bw/day) prior to S9 preparation on the fourth day.

The test article, N-butylpyrrolidone (CAS Reg. No 3470-98-2), was tested up to cytotoxic concentrations of 705.6 and 1411.2 µg/mL in the absence of activation and with a 24-hour treatment interval (experiment 2) that reduced cell growth to 57 and 22% that of the corresponding solvent controls, respectively. In experiment 1 (both without and with S9-mix) and in experiment 2 (with S9-mix) there was little if any cytotoxicity and no precipitation; thus the limit concentration of the assay (10 mM), would apply to them. No significant increase in mutant frequency over that of the solvent controls was observed for any test article concentration without or with activation in either mutation experiment. The positive controls did induce the appropriate responses. **There was no evidence of induced mutant colonies over background.**

***In Vitro* Mammalian Cell Micronucleus Test**

In an *in vitro* induction of micronuclei in cultured human peripheral blood lymphocytes assay (MRID 49695118, Morris, 2014), human peripheral blood lymphocyte cultures were treated with n-butylpyrrolidone dissolved in MEM culture medium and exposed for 4 hours without and with activation (experiment 1) and for 24 hours without activation (experiment 2). No precipitation of the test article was observed under any test condition. In order to assess the cytotoxicity of the test

article to cultured human lymphocytes, the cytokinesis-block proliferative index (CBPI) was calculated for cultures treated with the test article, and the solvent and positive controls. A preliminary cytotoxicity study using concentrations of 0, 5.51, 11.03, 22.05, 44.1, 88.2, 176.4, 352.8, 705.6 and 1411.2 µg/mL showed no evidence of cytotoxicity in the 4-hour exposure groups in the absence and presence of S9-mix but demonstrated slight toxicity at the maximum concentration of 1411.2 µg/mL (10 mM, the limit concentration for this assay) in the 24-hour exposure group, with a 25% reduction in CBPI. The selection of the concentration levels to be used for the micronucleus analyses in experiments 1 and 2 were based on these results, and those concentrations were 0, 352.8, 705.6 and 1411.2 µg/mL.

In experiments 1 and 2, and only in the absence of S9-mix, there were modest reductions in the CBPI of 22% and 24%, respectively, at the maximum concentration of 1411.2 µg/mL. (The exposure duration in experiment 2 was much longer, namely 24 hours.) **There were no statistically significant increases in the frequencies of micronucleated human lymphocytes after treatment with N-butylpyrrolidone** for 4 hours without or with activation or after treatment for 24 hours without activation up to the limit concentration of 1411.2 µg/mL. All positive and vehicle controls produced the expected results, with the positive controls inducing large increases in micronucleus frequencies that were statistically significant.

Neurotoxicity

There were no studies/data directly related to the possible neurotoxicity of 2-pyrrolidinone, 1-butyl. However, evidence of potential neurotoxicity was not observed in functional observation battery (FOB) performed in the 90-day oral toxicity study in the rat. Therefore, pyrrolidinone, 1-butyl is not expected to be neurotoxic.

Immunotoxicity

There were no studies/data directly related the immunotoxic potential of 2-pyrrolidinone, 1-butyl. However, thymic atrophy was observed at >100 mg/kg/day in rats treated with 2-pyrrolidinone, 1-butyl for 90 days via gavage.

Metabolism

There were no studies/data directly related to the metabolism, of 2-pyrrolidinone, 1-butyl.

V. TOXICITY ENDPOINT SELECTION

For purposes of risk assessment, the Agency utilizes the toxicity point of departure identified in the developmental toxicity study in rats. Since there was a large dose spread, the benchmark dose modeling (BMD) assessment (MRID 49695121) was conducted. The average benchmark model lower confidence limit (BMDL) is 201 mg/kg/day for a 5 % response which was based on a 5 % decreased fetal body weight. An uncertainty factor of 10X is applied for interspecies extrapolation and an uncertainty factor of 10X is applied for intraspecies variation. The Agency's level of concern is for Margins of Exposure (MOE) less than 100. There was a decrease in body weights in maternal animals on GD7 in the developmental toxicity study in rats, however this effect which was not considered suitable for acute dietary exposure assessment since the body

weights returned back to nearly normal on GD8. The toxicological endpoint is used for short-term, intermediate-term as well as chronic exposures. There were no data to suggest different points of departure for intermediate-term or chronic exposures.

VI. SPECIAL CONSIDERATIONS FOR INFANTS AND CHILDREN

Section 408 of the FFDCA provides that EPA shall apply an additional margin of safety for infants and children in the case of threshold effects to account for prenatal and post natal toxicity and the completeness of the database on toxicity and exposure unless EPA determines that a different margin of safety will be safe for infants and children. EPA concludes that an additional uncertainty factor (UF) is not necessary.

i. The database is considered adequate for FQPA assessment. The following acceptable studies are available:

90-Day Oral toxicity study in the rat (1)

Developmental toxicity study via the oral route of exposure in the rat (1)

ii. A developmental toxicity study in rats was available with 2-pyrrolidinone, 1-butyl. Fetal susceptibility was not observed. Maternal and developmental toxicity were observed at the same dose, 500 mg/kg/day, the highest dose tested. There are no concerns for the lack of 2-generation reproduction study because the male and female reproductive parameters were evaluated in the 90-day study and no evidence of fetal susceptibility was seen in the rat developmental toxicity study in rats.

iii. There were no studies/data directly related to the possible neurotoxicity of 2-pyrrolidinone, 1-butyl. However, evidence of potential neurotoxicity was not observed in functional observation battery (FOB) performed in the 90-day oral toxicity study in the rat. Therefore, pyrrolidinone, 1-butyl is not expected to be neurotoxic.

iv. There were no studies/data directly related the immunotoxic potential of 2-pyrrolidinone, 1-butyl. Thymic atrophy was observed at >100 mg/kg/day in rats treated with 2-pyrrolidinone, 1-butyl in the 90-day oral toxicity study, however, these microscopic changes in the thymus are considered as an adaptive response and not an adverse effect.. EPA has concluded that an immunotoxicity study is not required at this time.

v. The dietary food exposure assessment utilizes proposed tolerance level or higher residues and 100% CT information for all commodities. In addition, a conservative drinking water concentration value of 100 parts per billion (ppb) was used to assess the contribution to drinking water. By using these screening-level assessments, chronic exposures/risks will not be underestimated.

Taking into consideration the available information, EPA concludes the additional 10X FQPA safety factor be reduced to 1X.

VII. EXPOSURE

The request is for the establishment of a tolerance exemption for residues of 2-pyrrolidinone, 1-butyl- for use under 40 CFR 180.920 at a maximum formulation concentration not to exceed 30 % w/w. Human exposures to 2-pyrrolidinone, 1-butyl- applied as such are primarily expected to be those persons occupationally exposed by the inhalation and dermal routes of exposure by virtue of agriculturally associated activities involving pesticide application and related activities. Persons not occupationally exposed due to work activities may be exposed via the oral route of exposure to possible pesticide residues on treated crop commodities. Although non-occupational exposures are not expected based on the proposed use the Agency conducted a screening level assessment of “residential” pesticide handler exposure and risk as well as possible post-application exposures. Non-dietary exposures are expected to be short-term exposures according to SOP for assessing occupational and residential exposures.

Dietary exposure is estimated using the Agency’s Dietary Exposure Estimate Model (DEEM) (results attached). Estimated dietary exposures do not exceed the Agency’s level of concern. The most highly exposed subpopulation is children 1-2 years old. The estimated dietary exposure to the children 1-2 years old is 0.424 mg/kg/day which equates to 21.1% of the cPAD. The estimated dietary exposure to the total U.S. Population is 0.114 mg/kg/day which equates to 5.7% of the cPAD.

In conducting the chronic dietary exposure assessment, EPA used food consumption information from the U.S. Department of Agriculture’s (USDA’s) 2003-2008 National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA). As to residue levels in food, no residue data were submitted for acetic acid. In the absence of specific residue data, EPA has developed an approach which uses surrogate information to derive upper bound exposure estimates for the subject inert ingredient. Upper bound exposure estimates are based on the highest tolerance for a given commodity from a list of high use insecticides, herbicides, and fungicides. A complete description of the general approach taken to assess inert ingredient risks in the absence of residue data is contained in the memorandum entitled “Alkyl Amines Polyalkoxylates (Cluster 4): Acute and Chronic Aggregate (Food and Drinking Water) Dietary Exposure and Risk Assessments for the Inerts,” (D361707, S. Piper, 2/25/09) and can be found at <http://www.regulations.gov> in docket ID number EPA-HQ-OPP-2008-0738.

In the dietary exposure assessment, the Agency assumed that the residue level of the inert ingredient would be no higher than the highest tolerance for a given commodity. Implicit in this assumption is that there would be similar rates of degradation (if any) between the active and inert ingredient and that the concentration of inert ingredient in the scenarios leading to these highest levels of tolerances would be no higher than the concentration of the active ingredient.

The Agency believes the assumptions used to estimate dietary exposures lead to an extremely conservative assessment of dietary risk due to a series of compounded conservatisms. First, assuming that the level of residue for an inert ingredient is equal to the level of residue for the active ingredient will overstate exposure. The concentrations of active ingredient in agricultural

products are generally at least 50 percent of the product and often can be much higher. Further, pesticide products rarely have a single inert ingredient; rather there is generally a combination of different inert ingredients used which additionally reduces the concentration of any single inert ingredient in the pesticide product in relation to that of the active ingredient.

Second, the conservatism of this methodology is compounded by EPA's decision to assume that, for each commodity, the active ingredient which will serve as a guide to the potential level of inert ingredient residues is the active ingredient with the highest tolerance level. This assumption overstates residue values because it would be highly unlikely, given the high number of inert ingredients, that a single inert ingredient or class of ingredients would be present at the level of the active ingredient in the highest tolerance for every commodity. Finally, a third compounding conservatism is EPA's assumption that all foods contain the inert ingredient at the highest tolerance level. In other words, EPA assumed 100 percent of all foods are treated with the inert ingredient at the rate and manner necessary to produce the highest residue legally possible for an active ingredient. In summary, EPA chose a very conservative method for estimating what level of inert residue could be on food, then used this methodology to choose the highest possible residue that could be found on food and assumed that all food contained this residue. No consideration was given to potential degradation between harvest and consumption even though monitoring data shows that tolerance level residues are typically one to two orders of magnitude higher than actual residues in food when distributed in commerce.

Accordingly, although sufficient information to quantify actual residue levels in food is not available, the compounding of these conservative assumptions will lead to a significant exaggeration of actual exposures. EPA does not believe that this approach underestimates exposure in the absence of residue data.

Residential Exposure

The Agency expresses Level of Concern (LOC) as Margin of Exposure (MOE) < 100. The MOE is the ratio of estimated daily dose to the toxicological endpoint used for risk assessment. Both are expressed as mg/kg/day and the result is unitless. Margins of exposure in the screening level assessment are all > 100 and therefore do not exceed the Agency's level of concern. Results of the screening level assessment are presented in the Attachment.

There is uncertainty regarding the possibility of "residential" use of this inert. The Agency conducted a "screening" level assessment of pesticide application activities known to result in high exposures, relatively speaking. The "home-owner" pesticide handlers are assumed to wear short-pants, short-sleeved shirts and shoes plus socks but no protective gloves. Dermal and inhalation exposure are assumed to be 100%. Thus the resulting estimates of risk are considered conservative, i.e. protective.

Convention Used to Estimate Exposure =
Unit Exposure * Application rate * Units Treated ÷ Body weight

Table 3.0 Estimated Residential Pesticide Handler (Mixer/Loader/Applicator) Exposure and Risk For Outdoor Uses

Mixer/loader/applicator	Unit Exposure mg/lb handled	Application Rate lb/gal	Units Treated Acres/day	Body weight kg	Average Daily Dose mg/kg/day	Margin of Exposure
Hose end sprayer	Dermal 13.4 Inhal. 0.022	0.01056 lb/gal	5 gal/day	80 kg	Derm 0.00884 Inhal 0.00001452	22,702
Pump-up hand-held sprayer	Dermal 63 Inhal 0.018		5 gal/day		Derm 0.04158 Inhal 0.00001188	4832
Backpack sprayer	Dermal 130 Inhal 0.14		5 gal/day		Derm 0.0858 Inhal 0.0000924	2340

Factors used in residential exposure assessment:

Assumed 0.05% of formulation = inert.

Assumed product density 9.0 lb gal.

Assumed typical rate of application 3 fl oz formulation per gallon of finish spray

Assumed 5 gallon spray applied per day to ½ A for a typical residence

Body weight 80 kg from HED SOP

Dermal absorption = 100 %, inhalation absorption 100 %

Unit Exposures from Standard Operating Procedures for Residential Pesticide Exposure

Assessment Health Effects Division/ OPP January 2012.

Toxicological Endpoint NOAEL 201 mg/kg/day

Margin of Exposure = NOAEL mg/kg/day ÷ Average Daily Dose mg/kg/day. Since the same toxicological endpoint is used for dermal and inhalation and was identified from the same study, the dermal and inhalation exposures are summed prior to dividing into the NOAEL. HED SOP

9 lb/gallon formulation * 0.05 (per cent inert) = 0.45 lb inert/gallon formulation

0.45 lb inert/gal formulation ÷ 128 fl oz /gal formulation = 0.00352lb inert/fl oz

3 fl oz per gallon spray * 0.00352 lb inert/ fl oz = 0.01056 lb inert per gallon of finish spray

For five gallons finish spray per day = 0.0528 lb inert per day for ½ acre (**therefore = 0.1056 lb inert per acre**)

Margin of Exposure = NOAEL/Average Daily Exposure (dermal and inhalation exposures are summed prior to division into NOAEL).

Table 4.0 Estimated Residential Handler Indoor Exposures and Risks

Mixer/loader/applicator	Unit Exposure mg/lb handled	Amount (lbs) Handled/day	Body weight kg	Average Daily Dose mg/kg/day	Margin of Exposure
Mopping	Dermal 71.6	0.0065	80 kg	Derm 0.0058	35,000

	Inhal. 2.38		Inhal 0.00019	1.1M
Wiping	Dermal 2870 Inhal 67.3	0.00085	Derm 0.0304 Inhal 0.00072	6,600 280,000
Trigger pump spray	Dermal 220 Inhal 2.4	0.039	Derm 0.107 Inhal 0.00117	1400 126,000

For the mopping scenario, it was assumed that 1 gallon of diluted solution is used. RD assumes that cleaning products are assumed to have the same density as water (8.34 lbs/gallon). While typical product concentrate directions indicate that 1 oz concentrated product per 1 gallon of water should be used, RD followed the Antimicrobials Division SOP and assumed a dilution factor of 2 oz concentrated product/128 oz (1 gallon) of water for the residential handler risk assessment to represent heavy-duty cleaning formulations. Based on information from RD, the Agency assumed that the maximum percentage by weight of the inert ingredient in indoor products would be 5.0%.

1 gallon formulated pesticide solution * (8.34 lb/gal) * (5.0%) * (2 fl oz/128 fl oz dilution factor) = 0.0065 lb inert in formulated solution/ day

For wiping scenario

0.13 gallon formulated solution * (8.34 lb/gal) * (5.0%) * (2 fl oz/128 fl oz dilution factor) = 0.00085 lb inert in formulated solution/ day

For trigger pump spray

0.094 gallon formulated solution * (8.34 lb/gal) * (5.0%) = 0.039 lb inert in formulated solution/ day

RESIDENTIAL and RECREATIONAL POST-APPLICATION EXPOSURE

Table 5.0 Summary Recreational and Residential Post-Application Exposures and Risks		
Activity	Exposure (Dose) mg inert./kg/day	MOE
Toddler short-term oral hand to mouth from contacting treated turf	0.01835	10,954
Toddler oral object to mouth (turfgrass)	0.00115	175,000
Adult dermal post applic turf contact	0.249	807
Toddler dermal post applic turf contact	0.477	421
Adult golfer post app turf contact	0.0172	11,686
Child golfer post app turf contact	0.0292	6884
Toddler combined exposure	0.4965 = hand to mouth + object to mouth + turf post-application	405

Table 5.0 Summary Recreational and Residential Post-Application Exposures and Risks		
	exposure	

MOE = NOAEL ÷ Dose. NOAEL = 201 mg inert/kg/day.

Adult and Adolescent Golfer Post-Application Dermal Exposure may be estimated using the convention stated in Science Advisory Council for Exposure draft SOP regarding “Golfer Exposure Assessment For Adults and Children” (24 August 2000). The draft policy states that adult and adolescent golfer dermal post-application exposure may be calculated as $DE_{(t)}$ (mg a.i./kg bw/day) = $(TTR_{(t)} (\mu\text{g}/\text{cm}^2)) * TC (\text{cm}^2/\text{hr}) * \text{hr}/\text{day} / (CF (1000 \mu\text{g}/\text{mg})) \div BW$ (body weight (kg)) Where:

$DE_{(t)}$ = dermal exposure at time (t) attributable to golfing on previously treated turf (mg a.i./kg bw/day).

$TTR_{(t)}$ = turf transferable residue at time t ($\mu\text{g}/\text{cm}^2$)

TC = Transfer Coefficient (500 cm^2/hr)

hr = exposure period (4 hours)

CF = conversion factor to change μg to mg.

BW = body weight (kg) (80 kg for adult; adjusted (multiplied) by a factor of 1.7 for child golfers)

and where $TTR_t = AR * F * (1-D)^t * CF2 * CF3$

AR = application rate (lb inert/acre); 0.63 lb inert/acre (taken from Table 3.0 above where 0.315 lb is applied to $\frac{1}{2}$ acre)

DA = Dermal absorption 100%

F = fraction of inert available on turf/grass (unitless); 5%

D = fraction of residue that dissipates daily (unitless); 10

t = postapplication day on which exposure is being assessed;

CF2 = weight unit conversion factor to convert the lbs ai in the application rate to use for the DFR or GR value ($4.54\text{E}+8 \mu\text{g}/\text{lb}$)

CF3 = area unit conversion factor to convert the surface area units (acre) in the application rate to cm^2 for the TTR or GR value ($2.47\text{E}-8 \text{ acre}/\text{cm}^2$)

Therefore the $TTR = 0.1056 \text{ lb ai}/\text{A} * 0.05 (\%) * 4.54^8 \mu\text{g}/\text{lb} * 2.47^{-8} \text{ A}/\text{cm}^2 = 0.688 \mu\text{g}/\text{cm}^2$

$DE = 0.688 \mu\text{g}/\text{cm}^2 * 500 \text{ cm}^2/\text{hr} * 4 \text{ hr}/\text{day} * 0.001 \mu\text{g}/\text{mg} \div 80 \text{ kg} = 0.0172 \text{ mg inert}/\text{kg}/\text{day}$.

MOE for adult golfer is $201 \text{ mg}/\text{kg}/\text{day} \div 0.0172 \text{ mg inert}/\text{kg}/\text{day} = 11,686$.

The adult dose level is adjusted by a factor of 1.7 to estimate child golfer exposure therefore $0.0172 \text{ mg inert.}/\text{kg}/\text{day} * 1.7 = 0.0292 \text{ mg inert}/\text{kg}/\text{day}$.

MOE for child golfer is $201 \text{ mg inert/kg/day} \div 0.0292 \text{ mg inert/day} = 6884$

A MOE of 100 is adequate to protect golfers from dermal post-application exposures to treated golf course turf. Inhalation exposure is believed to be negligible. The proposed use does not exceed the Agency's level of concern.

Adult and toddler dermal post-application exposure to treated residential turf is assessed using SOP (2.2) which indicates that

$\text{PDR} = \text{TTR} * \text{TC} * \text{ET} * \text{conversion factor } \mu\text{g to mg} \div \text{kg bw}$ where:

Potential Dose Rate (PDR)

Turf Transferable Residue (TTR) ($0.688 \mu\text{g}/\text{cm}^2$)

TC = Transfer Coefficient (TC) ($14,500 \text{ cm}^2/\text{hr}$ for adult and $5,200 \text{ cm}^2/\text{hr}$ for child)

ET = exposure time (hours/day) (2)

CF = $0.001 \text{ mg}/\mu\text{g}$

Dermal absorption = 100%

Body weight = 80 kg for adult, 15 kg for toddler.

$0.688 \mu\text{g}/\text{cm}^2 * 14,500 \text{ cm}^2/\text{hr} * 2 \text{ hr/day} * 0.001 \text{ mg}/\mu\text{g} \div 80 \text{ kg bw} = 0.249 \text{ mg inert/kg/day}$ for adult.

$\text{MOE} = \text{NOAEL} \div \text{Dose and } 201 \text{ mg/kg/day} \div 0.249 \text{ mg/kg/day} = 807$

$0.688 \mu\text{g}/\text{cm}^2 * 5,200 \text{ cm}^2/\text{hr} * 2 \text{ hr/day} * 0.001 \text{ mg}/\mu\text{g} \div 15 \text{ kg bw} = 0.477 \text{ mg inert/kg/day}$ for toddler

$\text{MOE} = \text{NOAEL} \div \text{Dose and } 201 \text{ mg/kg/day} \div 0.477 = 421$

Children's short-term oral hand-to-mouth exposure =

$\text{TTR}_t * \text{SA} * \text{EX} * \text{FQ} * \text{ET} * \text{CF1}$ where:

PDR_t = potential dose rate on day "t" ($\text{mg}/\text{kg bw/day}$)

TTR_t = turf transferable residue on day "t" ($\mu\text{g}/\text{cm}^2$ turf); $0.00056 \mu\text{g}/\text{cm}^2$

SA = surface area of the hand (cm^2/event ; palmer surface area of 3 fingers = 20 cm^2)

EX = extraction factor from the hand by saliva = 50 %

FQ = frequency of hand-to-mouth activity (events/hr); 20 events/hr

ET = exposure time (hr/day); 2 hrs/day

CF1 = weight unit conversion factor to convert μg in the TTR value to mg for the daily exposure ($0.001 \text{ mg}/\mu\text{g}$).

$0.688 \mu\text{g}/\text{cm}^2 * 20 \text{ cm}^2/\text{event} * 0.50 \% \text{ extraction factor} * 20 \text{ events/hr} * 2 \text{ hr/day} * 0.001 \text{ mg}/\mu\text{g} \div 15 \text{ kg bw} = 0.01835 \text{ mg inert/kg/day}$.

$\text{MOE} = \text{NOAEL} \div \text{Dose } 201 \text{ mg inert/kg/day} \div 0.109 \text{ mg inert/day} = 10,954$.

Children's object-to-mouth (turfgrass) = Grt * IgR * CF1

PDR_t = potential dose rate on day "t" (mg/kg bw/day)

GRT = grass (and plant matter) residue on day "t"; 0.00056 µg/cm²

IgR = mouthing rate of grass (cm²/day); 25 cm²/day

CF1 = weight unit conversion factor to convert µg units of residue on the grass to mg for the daily exposure (0.001mg/µg).

$$0.688 \mu\text{g}/\text{cm}^2 * 25 \text{ cm}^2/\text{day} * 0.001\text{mg}/\mu\text{g} \div 15 \text{ kg bw} = 0.00115 \text{ mg inert}/\text{kg}/\text{day}$$

$$\text{MOE} = \text{NOAEL} \div \text{Dose and } 201 \text{ mg inert}/\text{kg}/\text{day} \div 0.00115 \text{ mg inert}/\text{kg}/\text{day} = 175,000.$$

Occupational Exposure

Since there is a large degree of uncertainty regarding the ultimate use(s) of 2-pyrrolidinone, 1-butyl- under 40 CFR 180.920, i.e., the submission is not specific as to target crops or methods of application etc., the Agency conducted a screening level assessment of occupational exposures and risks. As precedence for a screening level exposure assessment, the Agency follows the assessment of exposure to the amine oxides (Davis et al., 2009). The techniques are those developed by the Science Advisory Council for Exposure (ExpoSAC), Health Effects Division/OPP. The basic algorithm used is:

$$\begin{array}{ccccc} \text{Unit Exposure} * & \text{Application Rate} * & \text{Units Treated} \div & \text{Body Weight} = & \text{Estimated Daily Dose} \\ \text{mg/lb inert} & \text{lbs/unit} & \text{acres treated} & \text{kg} & \text{mg/kg/day} \\ \text{handled} & \text{(acre)} & \text{per day} & & \end{array}$$

For this assessment the Agency assumed dermal and inhalation absorption = 100%. Body weight is assumed to be 80 kg. Unit exposures are taken from the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table (rev Mar. 2013). USEPA / Office of Pesticide Programs / Health Effects Division. Rates of application and units treated are from the 2009 EPA assessment by Davis et al. The 2009 assessment is based on 30 % inert ingredient in pesticide formulations.

The Agency expresses Level of Concern (LOC) as Margin of Exposure (MOE) < 100. The MOE is the ratio of estimated daily dose to the toxicological endpoint used for risk assessment. Both are expressed as mg/kg/day and the result is unitless. Margins of exposure in the screening level assessment are all > 100 and therefore do not exceed the Agency's level of concern. Results of the screening level assessment are presented in the Attachment.

Table 6.0 ESTIMATED EXPOSURE/RISK OCCUPATIONAL APPLICATORS

Application method	Crop/Site	Dermal Unit Exposure	Inhalation Unit Exposure	Rate of Application	Units Treated	Dermal Dose	Inhalation Dose	Dermal MOE	Inhalation MOE
Aerial/liquid	Corn	0.0021	0.0000049	3.12	1200	0.0983	0.00023	2045	874,000
Airblast/liquid	Nut Trees	1.59	0.0047	2.16	40	1.717	0.0051	117	39,400
Groundboom liquid	Corn	0.0161	0.00034	3.12	200	0.126	0.0027	1595	74,000

Convention to calculate exposure and risk.

Unit Exposure (mg/lb inert handled) * Applic Rate (lb/A) * Units (A/day) * DA(%) ÷ body wt (80 kg) = Average Daily dermal or inhalation Dose (mg/kg/day)

Margin of Exposure = NOAEL (mg/kg/day) ÷ Average Daily Dose (mg/kg/day).

Rates of application taken from Davis et al 2009 (Davis et al assessment used 30 % concentration).

Dermal Absorption = 100%

Unit Exposures taken from Occupational Pesticide Handler Unit Exposure Surrogate Reference Table. U.S. Environmental Protection Agency, Office of Pesticide Programs. March 2013.

Unpublished. U.E. for applicators wearing a single layer of work clothing (long pants, long-sleeved shirt, shoes plus socks) and protective gloves (pilots no gloves) and no respiratory protection.

Table 7.0 ESTIMATED EXPOSURE/RISK OCCUPATIONAL MIXER/LOADERS

Application method	Crop/Site	Dermal Unit Exposure	Inhalation Unit Exposure	Rate of Application	Units Treated	Dermal Dose	Inhalation Dose	Dermal MOE	Inhalation MOE
Aerial/liquid	Corn	0.0376	0.000219	3.12	1200	1.76	0.0102	114	19,700
Airblast/liquid	Nut Trees			2.16	40	0.041	0.00024	4,900	837,500
Groundboom liquid	Corn			3.12	200	0.293	0.00171	686	118,500

VIII. AGGREGATE EXPOSURE

In estimating total dietary (food and drinking water) exposures to 2-pyrrolidinone, 1-butyl as an inert ingredient in pesticide formulations applied to growing crops the Agency uses the Dietary Exposures Evaluation Model – Food Commodity Intake Database (DEEM-FCID) model for chronic dietary exposures which presented as Attachment One. The DEEM analysis was conducted using the NOAEL noted earlier, 201 mg/kg/day, with the following uncertainty factors applied:

10X for interspecies extrapolation

10X for intraspecies variation

Margins of Exposure < 100 exceed the Agency's level of concern.

1. In evaluating dietary exposure to the 2-pyrrolidinone, 1-butyl, EPA considered exposure under the petitioned for exemptions from the requirement of a tolerance. EPA assessed dietary exposures as follows:

i. Acute exposure. No adverse effects attributable to a single exposure of 2-pyrrolidinone, 1-butyl were seen in the toxicity databases. Therefore, an acute dietary risk assessment for 2-pyrrolidinone, 1-butyl is not necessary.

Total Aggregate Exposure for an Adult (dietary, handler, post-application)

0.114 mg/kg/day the estimated dietary exposure to the "Total U.S. Population" (adult) is
5.7% of the cPAD

0.0858 mg/kg/day = highest residential handler exposure = backpack sprayer
0.249 mg/kg/day = post-application dermal exposure to treated lawn/turf
0.107 mg/kg/day = exposure from antimicrobial trigger pump spray
0.0172 mg/kg/day = adult golfer post-applications exposure.
0.573 mg/kg/day thus $201 \text{ mg/kg/day} \div 0.573 \text{ mg/kg/day} = 350$ Margin of Exposure

Total Aggregate Exposure to Child age 1-2 (dietary, post-application)

0.424 mg/kg/day the estimated dietary exposure to the most highly exposed subpopulation (toddlers 1-2 years) = 21.1% of the cPAD.
0.477 mg/kg/day = post-application dermal exposure to lawn/turf
0.01835 mg/kg/day = hand to mouth exposure
0.00115 mg/kg/day = object (turf grass) to mouth exposure
0.9205 mg/kg/day thus $201 \text{ mg/kg/day} \div 0.9205 \text{ mg/kg/day} = 218$ Margin of Exposure

EPA determines whether acute and chronic pesticide exposures are safe by comparing aggregate exposure estimates to the aPAD and cPAD. The aPAD and cPAD represent the highest safe exposures, taking into account all appropriate safety factors (SFs). EPA calculates the aPAD and cPAD by dividing the POD by all applicable UFs. For linear cancer risks, EPA calculates the probability of additional cancer cases given the estimated aggregate exposure. Short-, intermediate-, and chronic-term risks are evaluated by comparing the estimated aggregate food, water, and residential exposure to the POD to ensure that the MOE called for by the product of all applicable UFs is not exceeded. Based on the current petition, there are no residential uses for benzyl acetate nor is it expected to significantly contribute the overall risk due to its use in other consumer products. Therefore, an aggregate risk was conducted based on food and water only.

1. *Acute risk.* There was no hazard attributable to a single exposure seen in the toxicity database for 2-pyrrolidinone, 1-butyl. Therefore, 2-pyrrolidinone, 1-butyl is not expected to pose an acute risk.

2. *Chronic risk.* A chronic aggregate risk assessment takes into account exposure estimates from chronic dietary consumption of food and drinking water using the exposure assumptions discussed above for chronic exposure. The chronic dietary exposure from food and water to 2-pyrrolidinone, 1-butyl is 14.1% of the cPAD for the U.S. population and 52.7% of the cPAD for children 1-2 yrs old, the most highly exposed population subgroup.

3. *Aggregate cancer risk for U.S. population.* The EPA has not identified any concerns for carcinogenicity relating to 2-pyrrolidinone, 1-butyl.

4. *Short-term risk.* Short-term aggregate exposure takes into account short-term residential exposure plus chronic exposure through use in pesticide formulations applied to growing crops. The Agency has not identified any concerns regarding short-term risks.

Cancer. 2-pyrrolidinone, 1-butyl is not expected to be carcinogenic since there was no evidence of carcinogenicity in an oral toxicity study in rats, there is no target organ toxicity as well as the negative response for mutagenicity. Since the Agency has not identified any concerns for

carcinogenicity relating to 2-pyrrolidinone, 1-butyl, a cancer dietary exposure assessment was not performed.

IX. CUMULATIVE EXPOSURE

Cumulative effects from substances with a common mechanism of toxicity. Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide's residues and “other substances that have a common mechanism of toxicity.”

EPA has not found 2-pyrrolidinone, 1-butyl to share a common mechanism of toxicity with any other substances, and 2-pyrrolidinone, 1-butyl does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that benzyl acetate does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA's website at <http://www.epa.gov/pesticides/cumulative>.

X. ENVIRONMENTAL FATE & EFFECTS

Table 8.0

Test	Result	Reference
Biodegradability	Ready biodegradability (OECD 301D) Not readily biodegradable	Muckle, 2013a, MRID 49695104
	Inherent biodegradability (OECD 302B) Mean degradation = 81% (112 days)	Muckle, 2013b, MRID 49695105
Acute fish toxicity	<i>Oncorhynchus mykiss</i> (OECD 202) LC ₅₀ > 100 mg/L; NOEC 100 mg/L	Parr, 2014, MRID 49695106
Acute invertebrate toxicity	<i>Daphnia magna</i> (OECD 202) 24/48 hour EC ₅₀ > 100 mg/L 24/48 hour NOEC ≥ 100 mg/L	Muckle, 2013c, MRID 49695107
Invertebrate life cycle	<i>Daphnia magna</i> (OPPTS 850.1300) EC ₅₀ > 100 mg/L (immobilization, adult growth, reproduction) LOEC > 100 mg/L (immobilization, adult growth,, reproduction) NOEC = 100 mg/L (immobilization, adult growth, reproduction)	Sacker, 2014, MRID 49695108

Acute algal toxicity	<i>Pseudokirchneriella subcapitata</i> (OECD 201) Growth rate: EC ₅₀ > 160 mg/L; NOEC 40 mg/L; LOEC 80 mg/L Yield: EC ₅₀ 130 mg/L; NOEC 40 mg/L LOEC 80 mg/L	Vryenhoef, 2014, MRID 49695109
Environmental/ecological assessment	No/low aquatic toxicity; not expected to be persistent or To bioaccumulate; ultimately biodegradable.	

Biodegradation

Ready Biodegradability – 2-Pyrrolidinone, 1-butyl- was tested according to OECD Guideline Test 301D. Degradation was calculated by analysis of dissolved oxygen over 28-days. 2-pyrrolidinone, 1-butyl- was tested using a concentration of 2.08 mg/L with effluent from a sewage treatment plant used as inoculum. Sodium benzoate was used as the positive control. Biodegradation of the positive control was 67% after eight days and the criteria of validity were fulfilled. Biodegradation of 2-pyrrolidinone, 1-butyl- was not observed after 28 days. Therefore 2-pyrrolidinone, 1-butyl- was considered not readily biodegradable (Muckle, 2013a, MRID 49695104).

Inherent Biodegradability - 2-Pyrrolidinone, 1-butyl- was tested for biodegradability by aerobic elimination and degradation potential according to OECD Guideline Test 302B. Dissolved organic carbon (DOC) in the test vessels was measured twenty times over 112 days to analyze the degradation of 2-pyrrolidinone, 1-butyl- and the positive control. 2-Pyrrolidinone, 1-butyl- was tested at a concentration of 20 mg carbon/L (corresponding to 306.6 mg test item/L) with activated sludge from a sewage treatment plant used as inoculum. Aniline was used as the positive control. The test was prolonged to 112 days. Degradation of the positive control was 98% after eight days and the criteria for validity were met. Mean degradation of 2-pyrrolidinone, 1-butyl- was 81% at the end of the test with a lag phase for days 0-35 and degradation phase for days 36-112 (Muckle, 2013b, MRID 49695105).

Ecotoxicity

Acute Fish Toxicity – According to OECD Guideline Test 203, rainbow trout (*Oncorhynchus mykiss*) were exposed to 2-pyrrolidinone, 1-butyl- according to the threshold approach recommended by the European Chemicals Agency (ECHA). The test was conducted at a single concentration of 100 mg/L to ensure toxicity was not observed at this concentration. This was based on the EC₅₀ values for the acute toxicity to *Daphnia magna* and the algal growth inhibition test were greater than 100 mg/L. Seven fish were exposed to an aqueous solution of the test item at a single concentration of 100 mg/L for 96 hours at 14° C under semi-static conditions. The number of mortalities and any sub-lethal effects of exposure in each test vessel and control vessel were determined three and six hours after the start of exposure then daily for the remainder of the test (until 96 hours). Analysis of the 100 mg/L test preparation at 0 and 72 hours (fresh media) and at 24 and 96 hours (old media) showed measured test concentrations range from 88% to 95% of nominal. The results were based on nominal test concentrations only. Exposure to rainbow trout to 2-pyrrolidinone, 1-butyl- resulted in LC₅₀ value greater than 100 mg/L. The No Observed Effect Concentration (NOEC) was 100 mg/L. It was considered unnecessary and unrealistic to test at concentrations in excess of 100 mg/L (Parr, 2014, MRID 49695106).

Acute Invertebrate Toxicity – The acute toxicity to *Daphnia magna* from exposure to 2-pyrrolidinone, 1-butyl- was tested according to OECD Guideline Test 202. Twenty daphnids were exposed to 2-pyrrolidinone, 1-butyl- for 48 hours in a static system. Potassium dichromate was used as a positive control. The study was conducted as a limit test using 100 mg/L nominal concentration. After 24 and 48 hours, the immobilized daphnids were counted. None of the *Daphnia* were immobilized in the control. The treatment showed no toxicity. At the beginning of the test the content of 2-pyrrolidinone, 1-butyl- in the test solutions was determined using GC-determination. The recovery after 48 hours was 94% of the starting concentration and the correlation between nominal and measured concentration was good. The determination of biological results was based on the nominal concentration. The 24-hour and 48-hour NOEC for 2-pyrrolidinone, 1-butyl- was ≥ 100 mg/L. The 24-hour and 48-hour EC₅₀ for 2-pyrrolidinone, 1-butyl- was > 100 mg/L (Muckle, 2013b, MRID 49695105).

Invertebrate Life Cycle - The chronic toxicity of 2-pyrrolidinone, 1-butyl- to *Daphnia magna* was tested according to OPPTS Guideline Test 850.1300. Ten daphnids per dose group were exposed to an aqueous solution of 2-pyrrolidinone, 1-butyl- at concentrations of 1.0, 3.2, 10.0, 32.0, and 100 mg/L for 21 days. The test solutions were renewed three times per week. The number of live and dead adult daphnids and young *Daphnia* were recorded daily. Analysis of the 100 mg/L test preparation on Days 0, 5, 12, and 20 (fresh media) and on Days 2, 5, 7, 14, and 21 (old media) showed measured test concentrations to range from 80% to 94% of nominal value and so the results are based on nominal test concentrations. Measured concentrations of between less than the limit quantification determined to be 0.00051 mg/L for the analytical method used and 0.075 mg/L were obtained for the control group. While this represented a positive control, it was considered not to impact the test as no toxic effects were observed during the test and the measured concentrations obtained were minimal as compared to the test group. The EC₅₀ was > 100 mg/ml for immobilization adult growth and reproduction; the Lowest Observed Effect Concentration (LOEC) was > 100 mg/L for immobilization, adult growth and reproduction; and the NOEC was 100 mg/L for immobilization, adult growth and reproduction (Sacker 2014, MIRD 49695108).

Algal Acute Toxicity – The toxic effects of 2-pyrrolidinone, 1-butyl- on the growth of the freshwater blue-green alga *Pseudokirchneriella subcapitata* was investigated over 72 hours with methods similar to OECD Guideline Test 201. After a range finding study, *Pseudokirchneriella subcapitata* was exposed to aqueous solutions of the test material at concentrations of 10, 20, 40, 80 and 160 mg/L (three flasks/concentration) for 72 hours under constant illumination and shaking at $24 \pm 1^\circ$ C. Samples of the algal preparations were removed daily and cell concentrations determined for each control and treatment group using a Coulter® Multisizer Particle Counter. Analysis of the test preparation at 0 and 72 hours showed measured test concentrations to range from 92% to 112% of nominal. Therefore, the results were based on nominal test concentrations of 0.0014 mg/L which was less than the limit quantification (LOG) of the analytical method employed. Analysis of the control at 72 hours showed a measured concentration of 0.0016 mg/L and analysis of the duplicate sample taken showed a measured concentration of 0.0019 mg/L. Given the measured concentrations at 72 hours were just above the LOQ, and that no test item was detected at 0 hours it was considered that post-study contamination had occurred which had no impact on the study itself. The NOEC was determined to be 40 mg/L and the LOEC to be 80 mg/L.

for both growth rate and yield. The EC₅₀ was determined to be 130 mg/L for yield and > 160 mg/L for growth rate (Vryenhoef, 2014, MRID 49695109).

The biodegradability studies showed 2-pyrrolidinone, 1-butyl- is ultimately biodegradable. The octanol/water coefficient of 0.73 shows low potential for bioaccumulation. Acute fish toxicity LC₅₀ is greater than 100 mg/L and acute algal toxicity showed EC₅₀ values of 130 mg/L for yield and greater than 160 mg/L for growth. In two invertebrate studies the 24- and 48-hour EC₅₀ values > 100 mg/L. The invertebrate life cycle study showed an EC₅₀ > 100 mg/L for immobilization, adult growth and reproduction. From the preceding, it is concluded that 2-pyrrolidinone, 1-butyl- exhibits no to low toxicity to aquatic organisms and is not expected to bioaccumulate or be persistent in the environment.

XI. ENVIRONMENTAL JUSTICE

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," <http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

XII. HUMAN STUDIES

This assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide. These studies, listed below, have received the appropriate ethical review for use in risk assessment.

The PHED Task Force, 1998. The Pesticide Handler Exposure Database (PHED), Version 1.1. Task Force members: Health Canada, U.S. Environmental Protection Agency, the California Department of Pesticide regulation, and the American Crop Protection Association; released August 1998.

XIII. RISK CHARACTERIZATION

2-pyrrolidinone, 1-butyl exhibits very low acute oral and dermal toxicity to the rat. It is moderately irritating to the rabbit eye. It is slightly irritating to rabbit skin. It is not a skin sensitizer.

In a prenatal development study with 2-pyrrolidinone, 1-butyl- in rats, there were no treatment related toxic effects on embryogenesis or fetal development in doses up to 500 mg/kg/day. The fetal NOAEL for the study was determined to be greater than 500 mg/kg/day.

A benchmark modeling assessment was conducted on a prenatal developmental study in the rat. Based on the benchmark dose modeling, the NOAEL for risk assessment was identified. The BMDL of 201 mg/kg-day for a 5% response is chosen because the modeling was based on a BMR of 5% decreased fetal body weight.

A 90-day subchronic oral toxicity study was conducted with Wistar rats exposed to 2-pyrrolidinone, 1-butyl-, according to OECD Test Guideline 408. Oral administration of 2-pyrrolidinone, 1-butyl- to rats by gavage for a period of ninety consecutive days at dose levels of 10, 100, and 500 mg/kg/day. No treatment related adverse effects were observed. Several mutagenicity and genotoxicity studies indicate 2-pyrrolidinone, 1-butyl- is not genotoxic, clastogenic or mutagenic.

There were no studies directly related to the mammalian metabolism of 2-pyrrolidinone, 1-butyl- nor related to the possible neurotoxicity or immunotoxicity. However, there were no indications in the subchronic studies that would indicate the possibility of neurotoxicity or immunotoxicity.

Based on the lack of mutagenicity or genotoxicity and the similarity of 2-pyrrolidinone, 1-butyl- to N-methylpyrrolidone, it can be concluded that 2-pyrrolidinone, 1-butyl- should not be considered as potentially carcinogenic.

2-Pyrrolidinone, 1-butyl- exhibits low levels of toxicity to aquatic organisms (vertebrate, invertebrate, algae) and is biodegradable. It is not expected to bioaccumulate or to be persistent in the environment.

The mammalian toxicity and environmental fate and effects data are adequate to allow the Agency to derive a regulatory decision. Based on the toxicological information summarized earlier and based upon the Agency's screening level assessments of human exposure and risk, the Agency approves of 2-pyrrolidinone, 1-butyl as an inert ingredient (solvent/cosolvent) (CAS Reg. No. 3470-98-2) under 40 CFR 180.920 (Inert Ingredients used pre-harvest: exemptions from the requirements of a tolerance) at a maximum concentration not to exceed 30% w/w in pesticide formulations.

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ATTACHMENT

US EPA Ver. 3.16, 03-08-d
DEEM-FCID Chronic analysis for DEEM RESIDUE FILE FOR 2-PYRROLIDINONE, 1-BUTYL LIMIT 30% 1X SF
NHANES 2003-2008 2-day
Residue file name: C:\Users\dlieu\Documents\EPA RD Pesticides\Inerts\Reviews\2-Pyrrolidinone,
1-butyl - Mark Dow\DEEM for 2-Pyrrolidinone, 1-butyl Limitation 30.R08
Adjustment factor #2 used.
Analysis Date 08-30-2016/10:05:15 Residue file dated: 08-30-2016/10:03:16
Reference dose (RfD, Chronic) = 2.01 mg/kg bw/day
COMMENT 1: Inert 57 active ingredients + drinking water (100ppb)

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Total exposure by population subgroup

Population Subgroup	Total Exposure	
	mg/kg body wt/day	Percent of Rfd
Total US Population	0.113606	5.7%
Hispanic	0.124057	6.2%
Non-Hisp-White	0.111480	5.5%
Non-Hisp-Black	0.105571	5.3%
Non-Hisp-Other	0.134014	6.7%
Nursing Infants	0.148923	7.4%
Non-Nursing Infants	0.275840	13.7%
Female 13+ PREG	0.099143	4.9%
Children 1-6	0.328004	16.3%
Children 7-12	0.136446	6.8%
Male 13-19	0.080257	4.0%
Female 13-19/NP	0.081559	4.1%
Male 20+	0.084597	4.2%
Female 20+/NP	0.091897	4.6%
Seniors 55+	0.091612	4.6%
All Infants	0.236657	11.8%
Female 13-50	0.087842	4.4%
Children 1-2	0.423745	21.1%
Children 3-5	0.291381	14.5%
Children 6-12	0.150332	7.5%
Youth 13-19	0.080879	4.0%
Adults 20-49	0.086844	4.3%
Adults 50-99	0.091073	4.5%
Female 13-49	0.087800	4.4%

RDI: PV Shah, K. Leifer
M.I.Dow:S7958:PY1:(703)305-5533:IIAB:7505P